Applicants respectfully request reconsideration of the rejections of record in view of the foregoing amendments and the following remarks.

I. Alleged Lack of Enablement

Claims 1 to 47 have been rejected under 35 U.S.C. § 112, first paragraph for alleged lack of enablement. Applicants respectfully traverse the rejection because the Office Action has failed to meet its burden of establishing that the specification does not enable the subject matter defined by the present claims.

When making an enablement rejection, the Examiner bears the initial burden of establishing a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993). "[I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and ***to back up assertions of its own with acceptable evidence or reasoning*** which is inconsistent with the contested statement." *In re Marzocchi*, 439 F.2d 220, 224 (C.C.P.A. 1971)(emphasis added). Acceptable support for an enablement rejection can take the form of ***specific findings of fact, supported by the evidence***. M.P.E.P. § 2164.04.

Preliminarily, Applicants note that claims 13 to 20, 26 to 30, 38, and 44 to 47 have been cancelled. Claim 1 has been amended to recite, *inter alia*, a compound comprising uricase covalently bonded via a linking group to polyethylene glycol of a total weight average molecular weight of about 15,000 to about 30,000. Claim 21 has been amended to depend from claim 1, rather than from cancelled claims 13 to 20. Claim 22 has been amended to recite, *inter alia*, a method of enhancing the circulating half life of uricase comprising modifying the uricase by covalently bonding the uricase via a linking group to polyethylene

glycol of a total weight average molecular weight of about 15,000 to about 30,000. Claim 39 has been amended to recite, *inter alia,* a compound comprising uricase coupled to polyethylene glycol of a total weight average molecular weight of about 15,000 to about 30,000. Support for the amendments is found in the specification as filed at, for example, page 10, lines 13 to 18. No new matter has been added.

Applicants respectfully submit that the specification enables those skilled in the art to make and use the full scope of the subject matter defined by the present claims without undue experimentation, and the Office Action has failed to establish a reasonable basis to question the enablement provided for the subject matter defined by the claims. The Office Action acknowledges that the specification is enabling for PEG-5,000 or PEG-20,000 bound to uricase at unknown residues using a methoxy-SS-polyethylene glycol derivative, but asserts that the specification does not provide enablement for the full scope of the claimed subject matter. (Office Action dated November 19, 2002, page 2). The Office Action describes alleged deficiencies in the specification, but fails to explain why it doubts the truth or accuracy of the teachings provided in the specification. Moreover, the Office Action fails to support its assertions with acceptable evidence or reasoning. For example, the Office Action asserts that there is nothing in the specification indicating what effect using PEG of weight average molecular weights throughout the range of 10,000 to 30,000 would have. (Office Action dated November 19, 2002, page 2). The Office Action further asserts that the specification does not indicate what effect using the linking groups recited in claim 1 would have. *Id.*

The specification teaches, however, that uricase covalently bound to PEG of weight average molecular weight of from about 15,000 to about 30,000, and preferably of about 20,000, increases the circulating half-life of the uricase. (See, for example, page 10, lines 13

to 18 and page 11, line 30 to page 12, line 3). The specification also describes numerous biocompatible linking groups that can be used to covalently attach PEG to uricase. (See, for example, page 10, line 31 to page 11, line 15 of the specification as filed.). Notably, the specification states that "the particular linking groups do not appear to influence the circulating half-life of PEG-uricase or its specific enzyme activity." (See page 11, lines 22 to 23 of the specification as filed). Significantly, the Office Action has failed to provide any credible evidence or reasoning that establishes a reasonable basis to question the truth or accuracy of the statements provided in the specification.

In addition, the Office Action asserts, presumably with respect to claims 13 to 20, 38, and 44, that although the lysine residues listed in claim 20 are recited in the specification as places where the PEG is not to be attached, there is nothing in the specification that teaches where the PEGs are attached or what effect attaching or not attaching the PEG to these sites would have. (Office Action dated November 19, 2002, page 2). Without conceding the correctness of this assertion, claims 13 to 20, 38, and 44 have been cancelled, obviating the rejection with respect to these claims.

Finally, the Office Action asserts that there is nothing in the specification that teaches the embodiment recited in claims 26 to 30 and 45 to 47. (Office Action dated November 19, 2002, page 3). Without conceding the correctness of this assertion, claims 26 to 30 and 45 to 47 have been cancelled, obviating the rejection with respect to these claims.

Applicants respectfully submit that the Office Action has failed to meet its burden of establishing that the subject matter defined by claims 1 to 12, 21 to 25, and 31 to 44 is not enabled by the specification. Applicants accordingly, respectfully request withdrawal of the rejection.

II. Alleged Anticipation and/or Obviousness

A. Claims 1 to 5, 7, 13 to 21, 39, and 44 have been rejected under 35 U.S.C. § 102(a) as anticipated by, or, in the alternative, under 35 U.S.C. § 103(a) as obvious over, Caliceti, P., *et al.*, *Bioconjugate Chem* 12:515-522 (2001) (hereinafter "the Caliceti reference"). Applicants respectfully traverse the rejection because the Caliceti reference fails to teach or suggest every limitation of the present claims.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987); M.P.E.P. § 2131.

To establish *prima facie* obviousness, the PTO must satisfy three requirements. First, the Patent Office must provide ***objective evidence*** that the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, contains some suggestion or incentive that would have motivated those of ordinary skill in the art to modify a reference or to combine references. *In re Lee*, 61 U.S.P.Q.2d 1430, 1433 (Fed. Cir. 2002); *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1998). Second, the proposed modification or combination of the prior art must have had a reasonable expectation of success, determined from the vantage point of those of ordinary skill in the art, at the time the invention was made. *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991). Finally, the prior art reference or combination of references must teach or suggest all the limitations of the claims. *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970).

Applicants respectfully submit that the Caliceti reference fails to teach or suggest every limitation of the present claims, and the Office Action has failed to make of record any

objective evidence of a teaching or suggestion that would have led those of ordinary skill in the art to modify the reference's teachings.

The Caliceti reference describes uricase bound to branched monomethoxypoly(ethylene glycol) of 10,000 Da and also describes uricase bound to linear monomethoxypoly(ethylene glycol) of 5,000 Da. Abstract. The present claims recite uricase covalently bound to polyethylene glycol, wherein the polyethylene glycol has a total weight average molecular weight of about 15,000 to about 30,000. The Caliceti reference fails to teach or suggest uricase bound to PEG of an average molecular weight of about 15,000 to about 30,000. Accordingly, the Caliceti reference fails to teach or suggest every limitation of the present claims, and, therefore, fails to anticipate the claims. Applicants, accordingly, respectfully request withdrawal of the rejection under 35 U.S.C. § 102(a).

Moreover, the Office Action has failed to identify, and has thus failed to make of record, any evidence that those of ordinary skill in the art would have been motivated to modify the teachings of the Caliceti reference. In fact, those of ordinary skill in the art would ***not*** have been motivated to modify the reference's teachings. The Caliceti reference fails to teach or suggest uricase modified with polymers other than those described in the reference, including uricase modified with polyethylene glycol of an average molecular weight of about 15,000 to about 30,000. Accordingly, upon review of the Caliceti reference, those of ordinary skill in the art would not have been motivated to modify uricase with such polymers. Significantly, the Office Action has failed to offer any evidence to the contrary. The Office Action has, therefore, failed to establish *prima facie* obviousness and Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 103(a).

B. Claims 1 to 7, 13 to 21, 39, and 44 have been rejected under 35 U.S.C. § 103(a) as allegedly obvious over the Caliceti reference in view of U.S. Patent No. 4,460,683

(hereinafter "the Gloger patent"). Applicants respectfully submit that the rejection is deficient in that it is based on the assumption that the Caliceti reference teaches all the limitations of claims 1 to 7, 13 to 21, 39, and 44, except the limitation relating to the species from which the uricase is obtained. (Office Action dated November 19, 2002, page 4). Because, as noted above, this assumption is believed to be incorrect, Applicants respectfully request withdrawal of the rejection.

C. Claims 1 to 5, 8, 13 to 21, 39, and 44 have been rejected under 35 U.S.C. § 103(a) as allegedly obvious over the Caliceti reference in view of Chua, C., *et al.*, *Annals of Internal Medicine* 109:114-117 (1988) (hereinafter "the Chua reference"). Applicants respectfully submit that the rejection is deficient in that it is based on the assumption that the Caliceti reference teaches all the limitations of claims 1 to 5, 8, 13 to 21, 39, and 44, except the limitation relating to the species from which the uricase is obtained. (Office Action dated November 19, 2002, page 4). Because, as noted above, this assumption is believed to be incorrect, Applicants respectfully request withdrawal of the rejection.

D. Claims 1 to 7, 9 to 25, and 31 to 44 have been rejected under 35 U.S.C. § 103(a) as allegedly obvious over the Gloger reference in view of either U.S. Patent No. 4,179,337 (hereinafter "the Davis patent") or Zapilsky, *et al.*, *Topics in Applied Chemistry*, 347-370 (1992) (hereinafter "the Zapilsky chapter"). Applicants respectfully traverse the rejection because the Office Action has failed to establish *prima facie* obviousness.

As previously discussed, to establish *prima facie* obviousness, the Patent Office must provide ***objective evidence*** that the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, contains some suggestion or incentive that would have motivated those of ordinary skill in the art to modify a reference or to combine references. In addition, the Patent Office must demonstrate that the proposed

modification or combination of the prior art would have had a reasonable expectation of success, determined from the vantage point of those of ordinary skill in the art, at the time the invention was made.

Prior art references that serve as the basis of an obviousness rejection must be considered in their entirety, *i.e.*, the references must be considered ***as a whole***, including portions that would lead away from the claimed invention. M.P.E.P. 2141.02 (citing *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983)).

Applicants respectfully submit that, when the teachings of the Davis patent are considered as a whole, those of ordinary skill in the art would not have been motivated to combine the teachings of the Davis patent with those of the Gloger patent, and would not have had a reasonable expectation of success for the combination. The Office Action asserts that the Gloger patent teaches that uricase can be obtained from both *Candida utilis* and *Aspergillus flavus*. The Office Action further asserts that the Davis patent teaches that PEG of molecular weight ranging from 500 to 20,000 is preferred for conjugation to enzymes, and further asserts that the patent demonstrates that as the molecular weight of PEG conjugated to insulin increases, the activity of insulin also increases. (Office Action dated November 19, 2002, pages 4 to 5). The Office Action concludes that it would have been obvious to those of ordinary skill in the art to obtain uricase from the sources taught by the Gloger patent, and to conjugate the uricase to PEG of molecular weight of 10,000 to 20,000. (Office Action dated November 19, 2002, page 5). The Office Action further concludes that those of ordinary skill in the art would have expected that conjugating uricase to PEG of increasing molecular weight up to 20,000 would increase the activity of the uricase. *Id.* Applicants respectfully disagree and submit that, when the teachings of the Davis patent are considered as a whole,

the Davis patent fails to teach or suggest that conjugating an enzyme to PEG of increasing molecular weight increases the activity of the enzyme.

Applicants respectfully submit that those of ordinary skill in the art would not have been motivated to conjugate the uricase described in the Gloger patent to PEG of molecular weight of up to 20,000 because, upon review of the Davis patent, those of ordinary skill in the art would have expected such modification to decrease the specific activity of the uricase. With respect to the Office Action's assertion that the Davis patent teaches that as the molecular weight of PEG conjugated to insulin increases, the activity of insulin increases, Applicants respectfully point out that insulin is not an enzyme, but, rather, is a hormone. Accordingly, in contrast to the assertion made in the Office Action, the Davis patent fails to teach or suggest that the activity of ***an enzyme*** is increased when the enzyme is conjugated to PEG of increasing molecular weight. In fact, the Davis patent teaches the opposite, namely, that conjugating an enzyme to PEG of increasing molecular weight ***decreases*** the activity of the enzyme. (See col. 15, lns 37 to 45). Specifically, the Davis patent teaches that catalase conjugated to PEG 750 has a specific activity of 43,750 units/mg protein, while catalase conjugated to PEG 2000 has a specific activity of 43,500 units/mg protein. *Id.* The Davis patent, therefore, teaches that conjugating catalase to PEG of increasing molecular weight decreases the activity of the enzyme. Accordingly, upon review of the Davis patent, those of ordinary skill in the art would ***not*** have been motivated to conjugate the uricase described in the Gloger patent to PEG of molecular weight of up to 20,000 due to the expectation that doing so would decrease the specific activity of the uricase. The Office Action, therefore, has failed to provide credible evidence of a motivation, teaching, or suggestion that would have led those of ordinary skill in the art to combine the teachings of the Davis patent with those of the Gloger patent. In addition, the Office Action has failed to demonstrate that those of

ordinary skill in the art would have had a reasonable expectation of success for the combination. Accordingly, the Office Action has failed to establish *prima facie* obviousness, and Applicants respectfully request withdrawal of the rejection.

Applicants further respectfully submit that, when the teachings of the Zapilsky chapter are considered as a whole, those of ordinary skill in the art would not have been motivated to combine the teachings of the Zapilsky chapter with those of the Gloger patent, and would not have had a reasonable expectation of success for the combination. The Office Action asserts that the Zapilsky chapter teaches that PEG of molecular weight ranging from 2,000 to 20,000 is useful for modification of peptides and proteins, and further asserts that the patent demonstrates that as the molecular weight of PEG conjugated to alkaline phosphatase increases from 4,000 to 20,000, the activity of alkaline phosphatase also increases. (Office Action dated November 19, 2002, page 5). The Office Action concludes that it would have been obvious to those of ordinary skill in the art to obtain uricase from the sources taught by the Gloger patent, and to conjugate the uricase to PEG of molecular weight of 10,000 to 20,000. (Office Action dated November 19, 2002, page 5). The Office Action further concludes that those of ordinary skill in the art would have expected that conjugating uricase to PEG of increasing molecular weight up to 20,000 would increase the activity of the uricase. *Id.* Applicants respectfully disagree and submit that when the teachings of the Zapilsky chapter are considered as a whole, the chapter fails to teach or suggest that conjugating an enzyme to PEG of increasing molecular weight increases the activity of the enzyme.

Applicants respectfully submit that those of ordinary skill in the art would not have been motivated to conjugate the uricase described in the Gloger patent to PEG of molecular weight of up to 20,000 because, upon review of the Zapilsky chapter, those of ordinary skill

in the art would have expected such modification to decrease the specific activity of the uricase. Table I of the Zapilsky chapter shows the following:

PEG (MW)	**% native alkaline phosphatase activity**
m5000 [monofunctional]	66-44
m1900 [monofunctional]	97-55
4000 [bifunctional]	72
8000 [bifunctional]	70
20000 [bifunctional]	80

In addition, the description in the table states that "[m]odification [of alkaline phosphatase] with ***higher molecular weight mPEG gave more deactivation*** than did modification with the lower molecular weight mPEG. Modification with bifunctional PEG gave highly active protein conjugates and there ***was little dependence on molecular weight*** or degree of modification." (emphasis added). Accordingly, when the teachings of the Zapilsky chapter are considered as a whole, the chapter indicates that modification of the enzyme with higher molecular weight monofunctional PEG actually resulted in greater deactivation of the enzyme than did modification with lower molecular weight PEG. Furthermore, the reference teaches that the activity of the pegylated enzyme was only slightly affected by the molecular weight of the bifunctional PEG used to modify the enzyme.

Accordingly, upon review of the Zapilsky chapter, those of ordinary skill in the art would ***not*** have been motivated to conjugate the uricase described in the Gloger patent to PEG of molecular weight of up to 20,000 due to the expectation that doing so might decrease the specific activity of the uricase. The Office Action, therefore, has failed to provide credible evidence of a motivation, teaching, or suggestion that would have led those of ordinary skill in the art to combine the teachings of the Zapilsky chapter with those of the

Gloger patent. In addition, the Office Action has failed to demonstrate that those of ordinary skill in the art would have had a reasonable expectation of success for the combination. Accordingly, the Office Action has failed to establish *prima facie* obviousness, and Applicants respectfully request withdrawal of the rejection.

E. Claims 1 to 5, 8 to 25 and 31 to 44 have been rejected under 35 U.S.C. § 103(a) as allegedly obvious over the Chua reference in view of either the Davis patent or the Zapilsky chapter. Applicants respectfully traverse the rejection because the Office Action has failed to establish *prima facie* obviousness.

Applicants respectfully submit that, when the teachings of the Davis patent are considered as a whole, those of ordinary skill in the art would not have been motivated to combine the teachings of the Davis patent with those of the Chua reference, and would not have had a reasonable expectation of success for the combination. In addition, Applicants also respectfully submit that, when the teachings of the Zapilsky chapter are considered as a whole, those of ordinary skill in the art would not have been motivated to combine the teachings of the Zapilsky chapter with those of the Chua reference, and would not have had a reasonable expectation of success for the combination.

The Office Action asserts that the Chua reference teaches that uricase can be obtained from *Arthrobacter protoformiae*. The Office Action's assertions with respect to the Davis patent and Zapilsky chapter are described above. Applicants respectfully submit that, for the reasons stated above, upon review of either the Davis patent or the Zapilsky chapter, those of ordinary skill in the art would not have been motivated to conjugate the uricase described in the Chua reference to PEG of molecular weight of up to 20,000 due to the expectation that doing so would decrease the specific activity of the uricase. The Office Action, therefore, has failed to provide credible evidence of a motivation, teaching, or suggestion that would have

led those of ordinary skill in the art to combine the teachings of either the Davis patent or the Zapilsky chapter with those of the Chua reference. In addition, the Office Action has failed to demonstrate that those of ordinary skill in the art would have had a reasonable expectation of success for either combination. Accordingly, the Office Action has failed to establish *prima facie* obviousness, and Applicants respectfully request withdrawal of the rejection.

Conclusion

Applicant believes that the foregoing constitutes a complete and full response to the Office Action of record. Accordingly, an early and favorable Action is respectfully requested.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

Respectfully submitted,

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Date: February 11, 2003

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims

Claims 1, 21, 22, and 39 have been amended as follows.

1. (Amended) A compound comprising uricase covalently bonded via a linking group to polyethylene glycol, wherein the polyethylene glycol has a total weight average molecular weight of about [10,000] 15,000 to about 30,000, and wherein the linking group is selected from the group consisting of a succinimide group, an amide group, an imide group, a carbamate group, an ester group, an epoxy group, a carboxyl group, a hydroxyl group, a carbohydrate, a tyrosine group, a cysteine group, a histidine group and combinations thereof.

21. (Amended) The compound of [any one of claims 1 or 13-20] claim 1 wherein polyethylene glycol is covalently attached to uricase at one or more lysine residues.

22. (Amended) A method of enhancing the circulating half life of uricase comprising modifying said uricase by covalently bonding said uricase via a linking group to polyethylene glycol, wherein the polyethylene glycol has a total weight average molecular weight of about [10,000] 15,000 to about 30,000 and wherein the linking group is selected from the group consisting of a succinimide group, an amide group, an imide group, a carbamate group, an ester group, an epoxy group, a carboxyl group, a hydroxyl group, a carbohydrate, a tyrosine group, a cysteine group, a histidine group and combinations thereof.

39. (Amended) A compound comprising uricase coupled to polyethylene glycol, wherein the polyethylene glycol has a total weight average molecular weight of about [10,000] 15,000 to about 30,000.

Claims 13 to 20, 26 to 30, 38, and 44 to 47 have been cancelled.